

The independent risk factors of early diarrhoea in enteral nutrition for ICU patients

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Abstract

Objective: To investigate the prevalence of and factors associated with diarrhoea in the early stage of enteral nutrition in critically ill patients in intensive care units (ICUs).

Methods: This prospective, multicentre, observational study enrolled consecutive patients who were newly admitted to ICUs and received enteral nutrition treatment. Events were observed continuously for 7 days or until patients were transferred out of the ICU after enteral nutrition. Demographic and clinical data, enteral nutrition data, diarrhoea-related data and outcomes were recorded. A multivariate logistic regression analysis was used to analyse the risk factors for diarrhoea.

Results: The study included 533 patients, of whom 164 (30.8%) developed diarrhoea. Diarrhoea was most commonly observed on the first to third days after starting enteral nutrition treatment. The median (interquartile range) duration of diarrhoea was 2 (1–3) days. The administration of gastrointestinal prokinetic agents, the increase in acute physiological and chronic health scores and the pyloric posterior feeding method were independent risk factors for diarrhoea.

Conclusion: The increased severity of illness, the administration of gastrointestinal prokinetic agents and the pyloric posterior feeding method were independent risk factors for diarrhoea in critically ill ICU patients undergoing enteral nutrition treatment.

Keywords

Enteral nutrition, diarrhoea, critical illness, intensive care unit

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Introduction

Critically ill patients in the intensive care unit (ICU) are often accompanied by important metabolic changes, which are closely related to stress level, disease severity, injury mechanism, organ dysfunction and nutritional status.¹The metabolic response to stress or injury is characterized by increased release of cytokines, which leads to increased metabolism and excessive decomposition.² Increased protein hydrolysis, fat decomposition and hepatic glycogen decomposition result in reduced energy storage.² If nutritional support is not provided in time, the depletion of energy and protein will lead to a poor clinical prognosis.^{2,3}

Enteral nutrition (EN) is a feeding method used when the gastrointestinal function is working normally but the foods and nutrients cannot be taken orally. Compared with parenteral nutrition, EN is safe, effective, physiological, relatively simple and economical.⁴ It is increasingly widely used in clinics. Many studies have found that EN treatment for critically ill patients can reduce infection rate, ICU length of stay and mortality.^{5–7} EN protects gastrointestinal physiological function, prevents intestinal villus atrophy, reduces intestinal exudation, and promotes intestinal perfusion, thereby preventing ischaemia-reperfusion injury and protecting intestinal immune function.⁸

Although EN treatment is beneficial to critically ill patients, various feeding intolerance phenomena, including abdominal distention, excessive gastric residue, vomiting, reflux, diarrhoea and constipation, can occur during the implementation of EN treatment, ^{9,10} which seriously interfere with the effective implementation of EN treatment. Among them, diarrhoea is one of the most common manifestations of feeding intolerance and the rate of diarrhoea can be as high as 14–36% according

to different definitions and investigative methods.^{11–13} Diarrhoea can lead to EN interruption, a decrease in calorie and protein intake, secondary water and electrolyte balance disorders, damage of the skin mucosa, and an increase in patient mortality and ICU hospital costs.¹³ Simultaneously, it can also affect the patient's psychology and greatly increase the nursing workload.^{14–16} The concept of acute gastrointestinal injury (AGI) was proposed by the European Society of Intensive Care Medicine in 2012.¹⁷ Among the proposed concepts, it was suggested that AGI was secondary to diarrhoea, and the intestinal tract did not have complete digestive and absorptive functions and hence could not meet the body's needs for nutrients and water.17

At present, most of the epidemiological data about diarrhoea in critically ill patients in the ICU are from foreign studies, which probably do not reflect the actual situation in China.^{11,13,18,19}This current study aimed to investigate early diarrhoea during EN of ICU patients in several general hospitals in Zhejiang Province and to analyse the characteristics and influencing factors of diarrhoea, so as to provide reference for the effective prevention of diarrhoea during EN treatment in critically ill patients, hence improving nutritional treatment.

Patients and methods

Patient population

This prospective, multicentre, observational study was conducted in 29 ICUs in Zhejiang Province between 1 June 2016 and 31 October 2016. The study participants were consecutive patients newly admitted to the ICU and treated with EN. The inclusion criteria were as follows: (i) new ICU admissions >18 years; (ii) new EN treatment administered; (iii) ICU length of stay >2 days. The exclusion criteria were as follows: (i) presence of end-stage malignant tumours; (ii) previous diseases with diarrhoea symptoms (such as inflammatory bowel disease, irritable bowel syndrome); (iii) a history of digestive tract reconstruction; (iv) presence of acute digestive tract haemorrhage; (iv) incomplete survey data. The observation time was continuously for 7 days or until patients were transferred out of the ICU after EN was administered in the ICU.

Patients in this study provided written informed consent. The study protocol was approved by the Ethical Oversight Committee of Taizhou Hospital of Integrated Traditional Chinese and Western Medicine in Zhejiang, Wenlin, Zhejiang Province, China (no. TZ2016014).

Data collection

According to the guidelines of the Bristol Stool Form Scale with regard to validating a novel chart,²⁰a questionnaire on diarrhoea status of critically ill patients during EN treatment in the ICU was developed and confirmed by veteran experts in critical care and nutrition. Each clinical unit selected specific personnel to be responsible for the investigation, conducted centralized training and issued questionnaires. The survey included the following: (i) information about the hospital and ICU, including the name of the hospital, the grade of the hospital, whether it was a teaching hospital, the number of approved beds, the type of ICU, the number of patients in the ICU in 2015, and the mean hospital bed days; information (ii) admission about the patients, including sex, age, height, weight, body mass index (BMI), ICU admission admission diagnosis, time, Acute Physiology and Chronic Health Evaluation II (APACHE II) score,²¹and Nutritional Risk Screening 2002 (NRS 2002) score,²² whether the patients used mechanical ventilation, whether the patients received

vasoactive drugs, and the patient's serum albumin level; (iii) information regarding nutritional therapy, including start time of EN, daily fluid volume of EN, daily calorie dose of EN, EN pathway (before or after the pylorus), EN infusion mode (continuous or intermittent infusion) and whether gastrointestinal prokinetic agents were administered; (iv) stool condition, including stool frequency and characteristics, and the qualitative results of routine leukocyte counts in the stool; (v) prognostic information, including duration of mechanical ventilation, ICU length of stay and prognoses after discharge (including transfer to general wards, transfer to other ICUs, automatic discharge without deterioration of illness and automatic discharge due to death or deterioration of illness).

Definition of diarrhoea-related indices

The research indices were defined as follows: (i) definition of diarrhoea: defecation frequency (\geq 3 times per day), stool volume (\geq 200 g per day) and stool characteristics (pasty or watery) (referring to the Bristol Stool Form Scale classification category 5–7), while meeting the above three conditions;²³(ii) infectious diarrhoea: diarrhoea caused by intestinal inflammation caused by various acute and chronic bacteria, viruses, fungi and parasites. Laboratory diagnosis was based on routine stool examination to assess leukocyte positivity or faecal culture of pathogenic bacteria.²⁴

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). All data were tested using a normality test. Normally distributed continuous data are expressed as mean \pm SD. Data not normally distributed are expressed as median and interquartile range (IQR). Categorical data are expressed as n (%). Data not normally distributed were compared using Mann–Whitney *U*-test. Categorical data were compared using χ^2 -test. The risk factors for diarrhoea were analysed using multivariate logistic regression analysis. A *P*-value < 0.05 was considered to be statistically significant.

Results

A total of 542 critically ill patients were enrolled in the study. As nine patients had incomplete data and were excluded from the analysis, 533 patients were included in the final analysis. During the study period, 369 patients (69.2%) did not have diarrhoea and 164 patients (30.8%) had diarrhoea.

Of the 533 patients, 354 (66.4%) were and 179 (33.6%) were female male (Table 1). The age ranged from 19 to 96 years and the median (IQR) value was 67 (51–79) years. The median (IQR) value of the APACHE II score was 18.0 (13.0-23.0) points. The median (IOR) value of the start time of EN was the first day (1-2) after ICU admission. The APACHE II score of patients in the diarrhoea group was significantly higher than that of the non-diarrhoea group (P=0.003). The proportions of patients who received vasoactive drugs and gastrointestinal prokinetic agents were significantly higher in the diarrhoea group compared with the non-diarrhoea group (P = 0.012)and P = 0.001, respectively). The proportion of patients who received EN treatment using a pyloric posterior feeding method was significantly higher in the diarrhoea group compared with the non-diarrhoea group (P = 0.037). Overall, there was a significant difference between the two groups with regard to ICU admission diagnosis (P=0.008). When each disease was analysed separately, the rates of cardiovascular diseases and trauma/burn were significantly lower in the diarrhoea group compared with the non-diarrhoea group (P = 0.048)and P = 0.035, respectively); and the rate of cardiopulmonary arrest was significantly higher in the diarrhoea group compared with the non-diarrhoea group (P = 0.015). The ICU length of stay, the mechanical ventilation time and the mortality rate significantly higher in the were diarrhoea group compared with the nondiarrhoea group (P < 0.0001, P = 0.003)and P = 0.016, respectively). There were no significant differences between the two groups with regard to age, sex, BMI, NRS 2002 score, serum albumin level, mechanical ventilation use, calorie dose of EN, fluid volume of EN, EN infusion mode, start time of EN, target calories and ICU hospital costs.

Of the 533 patients, 164 patients (30.8%) developed diarrhoea within 1 week of the start of EN treatment in the ICU. Diarrhoea was most common on the first to third days after the start of EN treatment. The median (IQR) duration of diarrhoea was 2 (1-3) days and the median (IQR) stool frequency was four (3-5) times per day. The proportion of new diarrhoea on the first day after the start of EN was 5.8% (31 of 533 patients). With the prolongation of ICU length of stay, the proportion of new diarrhoea decreased gradually, with the proportion of new diarrhoea being 2.4% (8 of 333 patients) on the seventh day. It should be noted that the study calculated the rate of new diarrhoea each day as the number of new cases of diarrhoea on that particular day relative to the number of patients in the hospital ICU on the same day. As time went by, some patients were transferred out of the ICU, so the number of patients in the hospital ICU on any particular day got smaller and smaller. There was a significant difference in the rate of new diarrhoea at different time-points (P < 0.001). The proportion of patients with new diarrhoea on the first to third days was significantly higher than

			Diarrhoea	
Characteristic	Total	Non-diarrhoea	group	Statistical
	11 - 555	gi oup 11 – 307	11-104	significance
Age, years	67 (51–79)	66 (51–78)	69 (52–80)	NS
Sex				NS
Male	354 (66.4)	244 (66.1)	110 (67.1)	
Female	179 (33.6)	125 (33.9)	54 (32.9)	
BMI, kg/m²	22.0 (19.5–23.9)	21.6 (19.3–23.9)	22.3 (19.7–23.9)	NS
APACHE II score	18.0 (13.0–23.0)	17.0 (12.0–22.0)	19.0 (15.0–24.0)	P = 0.003
NRS 2002 score	4.0 (3.0–5.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	NS
Serum albumin, g/l	32.5 (28.4–36.5)	32.5 (28.4–36.7)	32.5 (28.5–36.3)	NS
ICU admission diagnosis				P = 0.008
Respiratory diseases	96 (18.0)	59 (16.0)	37 (22.6)	NS
Cardiovascular diseases	45 (8.4)	37 (10.0)	8 (4.9)	P = 0.048
Neurological lesions	142 (26.6)	99 (26.8)	43 (26.2)	NS
Digestive system diseases	9 (1.7)	7 (1.9)	2 (1.2)	NS
Postoperative	42 (7.9)	32 (8.7)	10 (6.1)	NS
Trauma/burn	118 (22.1)	91 (24.7)	27 (16.5)	P = 0.035
Severe sepsis	18 (3.4)	10 (2.7)	8 (4.9)	NS
Poisoning	20 (3.8)	10 (2.7)	10 (6.1)	NS
Cardiopulmonary arrest	13 (2.4)	5 (1.4)	8 (4.9)	P = 0.015
Others	30 (5.6)	19 (5.1)	(6.7)	NS
Vasoactive drugs				P = 0.012
Used	177 (33.2)	110 (29.8)	67 (40.9)	
Unused	356 (66.8)	259 (70.2)	97 (59.1)	
Mechanical ventilation				NS
Used	432 (81.1)	294 (79.7)	138 (84.1)	
Unused	101 (18.9)	75 (20.3)	26 (15.9)	
EN pathway				P = 0.037
Gastric feeding	466 (87.4)	330 (89.4)	136 (82.9)	
Post-pyloric feeding	67 (12.6)	39 (10.6)	28 (17.1)	
EN calories, kcal	900 (707-1168)	900 (707-1146)	900 (707–1286)	NS
EN fluid volume, ml	929 (743–1017)	917 (743–1027)	929 (725-1000)	NS
EN infusion mode				NS
Continuous	435 (81.6)	296 (80.2)	139 (84.8)	
Intermittent	98 (18.4)	73 (19.8)	25 (15.2)	
Gastrointestinal prokinetic agents				P = 0.001
Used	237 (44.5)	147 (39.8)	90 (54.9)	
Unused	296 (55.5)	222 (60.2)	74 (45.1)	
EN start time				NS
≤ 48 h	457 (85.7)	319 (86.4)	138 (84.1)	
	76 (14.3)	50 (Ì3.6)	26 (15.9)	
Target calories		· /		NS
Reached	121 (22.7)	83 (22.5)	38 (23.2)	
Not reached	412 (77.3)	286 (77.5)	126 (76.8)	
Mechanical ventilation time, days	5.0 (2.0-8.0)	5.0 (2.0-8.0)	6.0 (3.0–10.0)	P = 0.003

Table 1. Clinical and demographic characteristics of critically ill patients (n = 533) that underwent enteral nutrition in an intensive care unit that were included in this study.

(continued)

Characteristic	Total n = 533	Non-diarrhoea group <i>n</i> = 369	Diarrhoea group n = 164	Statistical significance ^a
ICU hospital stay, days ICU hospital cost, 10 000 Chinese Yuan	10.0 (6.0–15.0) 4.3 (2.8–7.6)	9.0 (6.0–13.0) 4.3 (2.6–7.6)	11.0 (8.0–18.0) 4.4 (3.1–7.7)	P < 0.001 NS
Discharge outcome Death Survival	92 (17.3) 441 (82.7)	54 (14.6) 315 (85.4)	38 (23.2) 126 (76.8)	P = 0.016

Table I. Continued

Data presented as median (interquartile range) or n of patients (%).

^aCategorical data were compared using χ^2 -test. All data that were not normally distributed are presented as median and interquartile range and compared using Mann–Whitney *U*-test. The *P*-values are the comparison between the diarrhoea and non-diarrhoea groups. NS, no significant between-group difference ($P \ge 0.05$).

The EN calorie value was the mean daily supplement EN calorie during the observation period; EN fluid volume was the mean daily supplement EN fluid volume during the observation period. The time to reach the target calorie was the 7th day after starting EN or the time to transfer out of ICU during the observation period.

BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; NRS 2002, Nutritional Risk Screening 2002; ICU, intensive care unit; EN, enteral nutrition.



Figure 1. The proportion of critically ill patients (n = 164) that developed new diarrhoea following enteral nutrition in an intensive care unit.

that on the fourth to seventh days (P < 0.05) (Figure 1). Among the 533 patients, 22 (4.1%) patients had positive results in routine stool leukocyte counts and infectious diarrhoea accounted for 13.4% (22 of 164 patients) of the total

number of diarrhoea patients. When patients were stratified according to the ICU admission diagnosis, the highest incidence rate of diarrhoea was 61.5% (8 of 13 patients) in patients with cardiopulmonary arrest and the lowest incidence of diarrhoea was 17.8% (8 of 45 patients) in patients with cardiovascular diseases. There was a significant difference in the incidence rate of diarrhoea across the different diseases (P < 0.05) (Figure 2).

A multivariate logistic regression analysis was used to determine the characteristics associated with the risk of diarrhoea following EN treatment. The results revealed that the administration of gastrointestinal prokinetic agents, the increase of APACHE II score and the pyloric posterior feeding method were independent risk factors for diarrhoea: odds ratios (95% confidence interval) were 1.82 (1.24, 2.65), 1.04 (1.02, 1.07) and 1.90 (1.11, 3.26), respectively (Table 2).

Discussion

The rate of diarrhoea in critically ill patients in ICUs has been reported to be 14– 36%.^{11–13} This current study observed a rate of diarrhoea of 30.8% (164 of 533) within 7 days of the start of EN treatment in critically ill patients. Diarrhoea was most common on the first to third days after the start of EN. The median (IQR) duration of diarrhoea was 2 (1–3) days. The difference in the rate of diarrhoea between this current study and previous studies may be due to the different research methods and definitions of diarrhoea was defined as follows: defecation frequency (\geq 3 times per day),



Figure 2. The proportion of critically ill patients (n = 164) that underwent enteral nutrition in an intensive care unit (ICU) that experienced diarrhoea stratified according to the ICU admission diagnosis. There was a significant difference in the incidence rate of diarrhoea across the different diseases (P < 0.05).

Table 2.	Multivariate	logistic	regression	analysis	of the	risk	factors	for	diarrhoea	in	critically il	I
patients (n = 533).											

Characteristic	В	Wald	OR	95% CI	Statistical significance
Use of gastrointestinal prokinetic agents	0.60	9.52	1.82	1.24, 2.65	P = 0.002
APACHE II score	0.04	10.73	1.04	1.02, 1.07	P = 0.00 I
EN pathway (post-pyloric feeding)	0.64	5.40	1.90	1.11, 3.26	P = 0.020

OR, odds ratio; CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; EN, enteral nutrition.

stool volume (≥ 200 g per day) and stool characteristics (pasty or watery) (referring to the Bristol Stool Form Scale classification category 5-7), while meeting the above three conditions.²³ The definition described the occurrence of diarrhoea in terms of defecation frequency and stool volume and characteristics. However, diarrhoea is defined as a diluted stool at least three times a day by the World Health Organization.²⁵ Therefore, the definition used in the current study was more precise than the latter in the definition of diarrhoea and more suitable for critically ill patients in the ICU. This current study focused on the observation of newly admitted ICU patients with EN for 1 week, which was shorter than the follow-up used in the other studies.^{11,13} Therefore, the rate of diarrhoea throughout the course of the disease might have been underestimated in the current study.

A total of 9331 patients were investigated in a previous study.¹⁹ Infectious diarrhoea was diagnosed according to the positive results of stool culture. Only 112 (9.3%) of the 1207 patients with diarrhoea were diagnosed as having infectious diarrhoea.¹⁹In this current study, 22 of the 164 patients (13.4%) with diarrhoea were diagnosed as having infectious diarrhoea. Therefore, the incidence rate of infectious diarrhoea within 1 week of the start of EN treatment was low with the following possible explanation: most critically ill patients in ICU cannot eat orally, so the nutrient solution was mainly fed through the nasal feeding tube, which would have reduced the chance of microbial invasion. Moreover, EN maintains intestinal integrity, avoids intestinal bacterial translocation and reduces the incidence of infection.⁸

This current study found that APACHE II score, EN pathway (the pyloric posterior feeding method) and the administration of gastrointestinal prokinetic agents were associated with the risk of diarrhoea following EN treatment. The administration of gastrointestinal prokinetic agents often cause diarrhoea by increasing the patient's gastrointestinal motility. Once the drug is discontinued, the diarrhoea also stops. In this current study, 90 (54.9%) patients with diarrhoea had received prophylactic gastrointestinal prokinetic agents before the start of EN treatment, which was one of the important causes of diarrhoea. The guidelines of the American Society for Parenteral and Enteral Nutrition in 2016 recommended that critically ill patients at high risk of aspiration should be administered with gastrointestinal prokinetic agents when clinically permitted to promote gastrointestinal motility.²⁶ Therefore, these current findings suggest that routine preventive administration of gastrointestinal prokinetic agents should be avoided in EN. Compared with the pyloric posterior feeding method, nutrient solution fed after the pylorus is not digested by gastric juices and is emptied by the pylorus, so diarrhoea is easily induced.²⁷ The guidelines of the American for Parenteral Society and Enteral Nutrition in 2016 recommended that critically ill patients were administered EN using the pyloric posterior feeding method when they were at a high risk of aspiration to reduce the incidence of aspiration and aspiration pneumonia.²⁶Therefore, in the presence of high-risk factors in the current study, pyloric feeding was used to reduce the incidence of diarrhoea, but pyloric feeding should not be routinely applied to each patient (with or without high-risk factors) for enteral nutrition. In this current study, the APACHE II score was selected as the severity score of the disease. The results showed that the risk of diarrhoea was positively correlated with the severity of the disease. The possible explanation for this was that critically ill patients experience a severe stress reaction and the gastrointestinal tract is the most sensitive organ that

undergoes a stress reaction, which could easily lead to gastroparesis, stress ulcer, gastrointestinal bacterial flora imbalance, organ dysfunction and internal environmental disorders. Therefore, compared with patients with low APACHE II scores, diarrhoea was more likely to occur in patients with high APACHE II scores.^{11,28–30}

Research has shown that the rate and duration of diarrhoea caused by intermittent transfusion of EN in critically ill patients were longer than those caused by continuous transfusion of EN.²⁹However, there was no correlation between the mode of transfusion of nutrient solution and diarrhoea in this current study. The possible explanation for this observation is that the types of diseases included in this study were not limited to trauma patients and the infusion speed during continuous infusion was not the same. Simultaneously, the results of this current study revealed that the rate of diarrhoea was not related to fluid volume of EN and calorie dose of EN. Therefore, more attention should be given to the selection of EN infusion rate and preparation type in the process of EN treatment. There are many types of EN preparations and diarrhoea was shown to be related to nutrient solution concentration, dietary fibre composition, protein sources (whole protein or short peptides) and energy density, which affects the accuracy of the results.³¹ This current study was a multicentre investigation. Considering the different EN nutrition pumps, heating modes and the indoor temperatures in different hospitals, the actual temperature of the nutrient solution could have varied greatly. Therefore, the type of EN preparation, whether heated and the specific heating temperature were not recorded in this current study. More randomized controlled trials are needed to demonstrate the effects of EN preparation types, whether heated, on diarrhoea in critically ill patients. For example, elemental formulas have been demonstrated to reduce the incidence of diarrhoea in gastrostomy-fed patients.

It has been reported that hypoproteinaemia is a risk factor for diarrhoea in critically ill patients.²³ Hypoproteinaemia lead to a decrease in colloid osmotic pressure and intestinal water reabsorption, which was more likely to lead to diarrhoea.³¹ However, no consistent conclusion has been reached in this current study. The possible reason was that the serum albumin level measured in this study was the value at admission and diarrhoea occurred several days after admission, so the admission values might not truly reflect the serum albumin levels during diarrhoea.

The relationship between diarrhoea and diseases has been described in the literature. For example, pancreatitis, endocrine disorders, cholecystitis and other diseases are associated with diarrhoea.²³The results of this current study demonstrated that the rate of respiratory and nervous system diseases was higher in patients with diarrhoea than the other diseases recorded. A multivariate logistic regression analysis revealed that there was no correlation between related diseases and diarrhoea. The possible reason was that the proportion of related diseases in the included patients was small, so no conclusion could be drawn about the relationship between related diseases and diarrhoea.

This current study had a number of limitations. First, this study was a multicentre, observational survey. The survey units were mainly tertiary hospitals and there were only four secondary hospitals. Therefore, the data did not represent the situation at non-tertiary hospitals. Secondly, the research cycle was relatively short, so the results of this study did not reflect the diarrhoea situation of the critically ill population as a whole. Thirdly, the results of faecal culture were not recorded during the onset of diarrhoea and infectious diarrhoea was only diagnosed by the qualitative analysis of routine stool leukocyte examination. Therefore, the rate of infectious diarrhoea in these patients was possibly underestimated. Fourthly, the clinical information collected in this study was not comprehensive and the relationship between EN preparation types, whether heated, during infusion and diarrhoea have not been studied. Therefore, the included risk factors in the assessment of diarrhoea risk were relatively small. However, the most common clinical indicators have been covered by possible risk factors currently collected.

In conclusion, this current study demonstrated that the rate of diarrhoea in critically ill patients within 1 week of the start of EN treatment in the ICU was 30.8%. Diarrhoea was most common in the first to third days after the start of EN. The median duration of diarrhoea was 2 days. The increased severity of illness, the administration of gastrointestinal prokinetic agents and the pyloric posterior feeding method were the independent risk factors for diarrhoea.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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